REMARKS

Disposition of Claims

4)☒ Claim(s) 1-34 is/are pending in the application.
4a) Of the above claim(s) 2,8,10-11,13-34 is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) 1,3-7,9,12 is/are rejected.

Claims 1, 6, 7 and 12 are currently amended, and new claims 35 and 36 are added. No new matter has been added.

New Claim 35 depends from currently amended claim 6 and recites that the "nucleic acid" encodes an HCN channel. New Claim 36 depends from claim 35 and stipulates that the HCN channel is HCN2. Support for these claims is found in the specification *inter alia* at paragraph [0035].

35 U.S.C. Section 112, second paragraph

The Examiner objected to the lack of clarity of claims 6, 7, 9 and 12 arguing that "it is unclear what is encompassed within the term gene." Various passages from the application describe adding a gene encoding a protein or peptide (specifically mentioned are Connexins and HCN) to hMSCs or HeLa cells, which encoded protein or peptide is expressed by the transfected cells:

> [0025] The method may further comprise a step of adding a gene to the mesenchymal stem cells by electroporation. The gene may encode for a connexin, such as connexin 40, connexin 43, and/or connexin 45. . . . .
> [0030] To further define the nature of the coupling hMSCs were co-cultured with human HeLa cells stably transfected with Cx43, Cx40, and $Cx45_7$ and it was found that hMSCs were able to couple to all these transfectants. . . . . .
>
> [0015] FIG. 3. Macroscopic properties of junctions in cell pairs between an hMSC and HeLa cell expressing only Cx40, Cx43 or Cx45. In all cases hMSC to Hela cell coupling was tested 6 to 12 after hours initiating co-culture.
>
> [0035] Alternatively, the hMSCs can be transfected to express genes that produce small therapeutic molecules capable of permeating gap junctions and influencing recipient cells. Further, for short term therapy, the small molecules can be directly loaded into hMSCs for delivery to recipient cells. The success of such an approach is dependent on gap junction channels as the final conduit for delivery of the therapeutic agent to the recipient

> cells. The feasibility of one such approach was demonstrated by transfecting hMSCs with mHCN2, a gene encoding the cardiac pacemaker channel, and delivering them to the canine heart where they generate a spontaneous rhythm.

It is undisputed that a gene is a nucleic acid and that the gene referred to in the present application encodes a protein or peptide (such as connexin and HCN), or "any small therapeutic molecules capable of permeating gap junctions and influencing recipient cells." In order to "influence the recipient cells," the encoded protein/peptide must be biologically active. To satisfy the Examiner's concerns, Applicants have amended claim 6 to delete "gene" and recite instead "a nucleic acid encoding a protein or peptide or biologically active fragment thereof." Claim 7 and claim 12 are amended to recite "nucleic acid" instead of "gene," and claim 9 depends on amended claim 7. New claim 35 recites "a nucleic acid" and New claim 36 depends from New claim 35.

Applicants point out that tie language "a nucleic acid encoding" was used in the allowed and issued claims Dr. Rosen's US patent 7,122,307 (entitled *High throughput biological heart rate monitor that is molecularly determined)* to describe "contacting a cardiac myocyte *in vitro* with an amount of a composition comprising a nucleic acid which encodes a[n] HCN channel and MiRP1. . . " See Claim 1.

Applicants respectfully submit that claims as amended overcome the Examiner's rejection and request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102(e) over Taheri et al.

Claims 1, 3-7 and 9 were rejected as anticipated by Taheri et al., U.S. Patent 6690970 (Taheri).

Applicants disagree that Taheri anticipates the cited claims. Applicants refer to the significant differences between the cited claims and Taheri that were pointed out in our response of 2/24/2010. Applicants respectfully submit that the Examiner incorrectly characterizes Taheri by saying that it describes "growing mesenchymal cells in culture and then attaching one end of the strip onto the atrium." This implies that the strip is formed first *in vitro* and then attached to the atrium. This is definitely not what happens in Taheri, nor does this reference even suggest the concept of forming a functional strip of conductive cells *in vitro* that could be then attached to the heart *in vivo*.

It is important to note that Taheri is focused on bypassing a specific, limited area in which a conduction block has been identified. FIG. 5 in Taheri "is a diagrammatic view showing a newly formed conductive cell bridge across an area of blockage in an AV node;" This is emphasized in Column 5, next to last paragraph of Taheri:

> After determination of the location of the ***block site*** 30 in FIG. 2, a plurality of the **implantation cells** 40 are implanted (seeded). Implantation may be performed by **injection** using the needle 34, but is preferably performed using the catheter described in more detail below. This same catheter is also preferably used for block site mapping, and may likewise be adapted for cell removal. As shown in FIG. 5, the implantation cells 26 **grow** to form a conductive cell bridge 50. One end of the cell bridge 50 connects to healthy tissue on one side of the block site 30 while the other end of the cell bridge connects to healthy tissue on the other side of the block site 30. The cell bridge 50 allows electric potential to pass through the block site 30 and reach the ventricular muscles.

As expressly stated above, Taheri injects individual "implantation cells," that then develop functional connections to one another in situ in the heart. Taheri is based on delivering a cells in suspension in a solution) (column 5, line 55, column 6 line 58, column 7 line 7, column 8 line 4, column 8, line 21), not a strip or syncytium of cells or cells on a biomaterial such as a microthread. Taheri does not implant a strip of cells grown culture. Moreover, seeded implantation cells cannot be and are never described as being sutured into place. To the extent that the injected cells form a strip, they form it in situ in the heart of the animal and not in culture. Indeed "injection" of cells is the only description offered for introducing the "implantation cells" to the animal's heart.

In complete contrast to Taheri, Brink et al. first make a functional, conducting strip of cells *in culture (in vitro)*, which strip is then implanted in the heart thereby forming the atrioventricular bypass tract of the present invention. Paragraphs 23, 24 and 27 of Brink explain:

[0023] According to the invention, a method of creating an atrioventricular bypass tract for a heart is provided, comprising growing mesenchymal stem cells into a strip with two ends, attaching one end of the strip onto the atrium of the heart, and attaching the other end of the strip to the ventricle of the heart, to create a tract connecting the atrium to the ventricle to provide a path for electrical signals generated by the sinus node to propagate across the tract and excite the ventricle.

[0024] The steps of attaching may be performed by suturing. The stem cells may be adult

human mesenchymal stem cells. The step of growing may comprise growing the stem cells in culture on a non-bioreactive material. The step of growing may be performed in an environment substantially free of any additional molecular determinants of conduction.

[0027] Human mesenchymal stem cells (Poietics.TM. hMSCs--Mesenchymal stem cells, Human Bone Marrow) were purchased from Clonetics/BioWhittaker (Walkersville, Md.) and cultured in MCS growing media and used from passages 2-4. Typical punctate staining for Cx43 and Cx40 was seen along regions of intimate cell to cell contact of the MSCs grown in culture as monolayers (FIGS. 1 A,B).

Brink also describes coculturing hMSCs with canine myocytes:

[0033] hMSCs were also co-cultured with adult canine ventricular myocytes. As shown in FIG. 4 the hMSCs couple electrically with cardiac myocytes. Both macroscopic (FIG. 4A) and multichannel (FIG. 4B) records were obtained. Junctional currents in FIG. 4A are asymmetric while those in FIG. 4B show unitary events of the size range typically resulting from the operation of homotypic Cx43 or heterotypic Cx43-Cx40 or homotypic Cx40 channels.sup.4,8. Heteromeric forms are also possible whose conductances are the same or similar to homotypic or heterotypic forms.

Figure 2 of Brink et al. shows that the human MSCs form gap junctions with one another in culture even before implantation, and that gap junction currents (Ij) passed between the connected cells.

> *[0014]FIG. 2. Macroscopic and single channel properties of gap junctions between hMSC pairs. Gap junction currents (Ij) elicited from hMSCs using symmetrical bipolar pulse protocol showed two types of voltage dependent current deactivation: (A)-symmetrical, (B): asymmetrical.*

In order to emphasize the distinction over Taheri that the "strip" is grown in culture before implantation, Applicants have amended Claim 1 to recite "growing mesenchymal stem cells *in vitro* into a strip with two ends." See also Paragraph [0034].

It is an important advancement over the prior art that the present bypass tract can be tested for the ability to conduct current before implantation. By contrast, the individual hMSCs suspended in a solution and injected into or near the site of a block still need grow *in situ* to form gap

junctions, and there is no guarantee that this will happen every time. With the present invention one does not even need to determine the location of the block with any specificity. It is enough to know that there is a block somewhere between the SA node and AV node that can then be bypassed with the implanted strip of the present invention. This in itself represents another improvement over Taheri and the other prior art.

A further advantage of the present invention is that implanting a functional syncytium (the strip) into the heart will return conductivity to the heart within a significantly shorter time than is needed for the injected cells of Taheri to "grow" *in situ*, connect and form a conductive bridge, with the inherent risk in Taheri that the syncytium of cells may not even function as intended because there is no way to test for this beforehand.

In the Rule 132 Declaration of Ira Cohen and Michael Rosen, we submit evidence that there is a 6-fold increase in efficiency of cell delivery when cells are grown *in vitro* into a strip such as on a nonreactive biomatrix, before implantation, compared to individual cells that are injected in a fluid medium.

Rejections under 35 U.S.C. § 102(e) over Rosen et al.

The Examiner rejected the cited claims under 35 U.S.C. § 102(e) over Rosen, US2004/0137621. Applicants submit herewith the Declaration of Michael R. Rosen, Richard B. Robinson and Ira S. Cohen and Peter Brink stating that any invention disclosed but not claimed in this reference was derived from the inventor of this application and is thus not the invention "by another."

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected Claims 1, 3-7, 9 and 12 as obvious under 35 U.S.C. § 103 based on *Taheri et al.* in view of Donahue *et al.* (US 2002/0155101). For the reasons set forth above, Applicants submit that Taheri does not teach or suggest key limitations of the present invention and these deficiencies are not compensated for by Donahue. Applicants therefore request that the Examiner withdraw this rejection.

Claims 1, 3-7, 9 and 12 were rejected as obvious under 35 U.S.C. § 103 based on the combination of Rosen and Donahue. However, as the Declaration states, any invention disclosed but not claimed in Rosen was derived from several inventors of this application.

Applicants respectfully submit that the present application, as amended, overcomes the objections and rejections of record and is in condition for allowance. Favorable consideration is respectfully requested. If any unresolved issues remain, it is respectfully requested that the Examiner telephone the undersigned attorney at (703) 622-6528 so that such issues may be resolved as expeditiously as possible. An interview with the Examiner and her supervisory is requested.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 504213 and please credit any excess fees to such deposit account.

Respectfully Submitted,

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Date

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